(c) administering the structurally altered Ig fusion protein of step (b) to the subject under conditions so that the structurally altered Ig fusion protein recognizes and binds the target thereby alleviating symptoms associated with the disease.

REMARKS

Claims 1-6 and 8-52 are pending. Claims 23-27 and 32-52 are withdrawn from consideration. Claims 1-6, 8-22 and 28-31 are presently under examination. Claim 7 has been cancelled. Sections of the Specification and Claims 1-6 have been amended. No new matter has been added.

The Examiner has reopened prosecution of the present case following the filing of an Appeal Brief on July 2, 2001 by Applicants. The Examiner has set forth new and/or modified grounds of rejection.

Attached hereto are marked-up pages captioned: "Appendix A: Amended Sections of Specification With Markings to Show Changes Made", "Appendix B: Amended Claims With Markings to Show Changes Made", and "Appendix C: Complete Set of Pending Claims".

Drawings

Applicants acknowledge that formal drawings will be required in this case when the application is allowed.

Objections to the Specification

The Examiner has objected to the specification for including trademarks which are not capitalized. Applicants have amended the specification accordingly.

The Examiner has also objected to the specification at page 48, line 25, stating that it is unclear what is meant by "previous patent". This is due to a typographical error and Applicants have amended the specification to refer to the provisional patent application from which the present application claims priority.

Section 112, second paragraph, Rejections

The Examiner has rejected Claims 1-3, 5-22 and 28-31 under 35 U.S.C. 112, second paragraph, as indefinite. Applicants respectfully submit that the cancellation of Claim 7 and amendments to Claims 1-3 and 5-6 obviate these rejections. Accordingly, withdrawal of these rejections is appropriate and respectfully requested.

Section 112, first paragraph, Rejections

The Examiner has rejected Claims 1-3, 5, 8-22 and 28-31 under 35 U.S.C. 112, first paragraph, as lacking written description. For the reasons set forth below, this rejection is respectfully traversed.

The claims have been amended to clarify that the present invention is directed to the alteration of multiple toxicity associated regions within the CH2 domain. As set forth by the Examiner, the art-recognized meaning of an immunoglobulin domain includes CH1, CH2, CH3 and possibly VH and VL domains. In the present specification, Applicants have specifically set forth two regions within the CH2 domain which are useful for reducing the toxicity of an immunoglobulin, namely, the regions defined by amino acids 231-238 and 310-331. Accordingly, in view of the amendments made herein, Applicants submit that withdrawal of this rejection is appropriate and is respectfully requested.

The Examiner has rejected Claims 1-22 and 28-31 under 35 U.S.C. 112, first paragraph, as being not enabled. For the reasons set forth below, this rejection is respectfully traversed.

The present invention is directed to a method of inhibiting immunoglogulin-induced toxicity resulting from immunoglobulin immunotherapy. As defined at page 9 of the present specification, "inhibiting immunoglobulin-induced toxicity" means to reduce or alleviate symptoms generally associated with toxicity caused by immunoglobulin or Ig fusion therapy. In short, the present invention is directed to altering an immunoglobulin to inhibit (including reducing and alleviating) the toxicity resulting from administration thereof, as compared to the toxicity resulting from administration of the unaltered immunoglobulin.

Example 3 of the present application shows how one skilled in the art is able to accomplish this, as acknowledged by the Examiner (Office Action, page 9, lines 1-4). However, Applicants respectfully submit that Example 3 is not "limited" to a demonstration that normal dogs administered with the CH2-deleted BR96 showed no acute GI toxicity, whereas dogs administered with the structurally altered BR96 antibody experienced typical GI toxicity, as alleged by the Examiner. Rather, Example 3 shows an example of how one skilled in the art can practice the claimed invention.

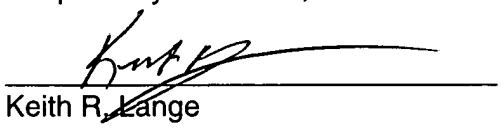
The Examiner's position appears to be that Applicants must show that administration of an altered immunoglobulin inhibits toxicity in a subject already exhibiting toxicity. However, this is not consistent with the clear definition of "inhibiting" set forth in the specification, namely to reduce or alleviate toxicity. In view of the argument presented herein, Applicants submit that withdrawal of this rejection is appropriate and is respectfully requested.

Conclusion

In view of the amendments and remarks above, Applicants submit that the claims are in condition for allowance and favorable action is therefore respectfully requested.

Should the Examiner have any comments or question regarding this reply, he is invited to contact the undersigned attorney.

Respectfully submitted,



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APPENDIX A: Amended Sections of Specification with Markings to Show Changes Made

Replacement paragraph at page 20, lines 7-10:

"In one example of the invention, the detergent can be a nonionic detergent. Examples of nonionic detergents include, but are not limited to, polysorbate 80 (also known as [Tween 80] TWEEN 80) or [(] polyoxyethylenesorbitan monooleate [), Brij] (also known as BRIJ) and [Triton] tetramethylbutylphenyl polymer with formaldehyde and oxirane (for example [Triton WR-1339 and Triton A-20] TRITON WR-1339 and TRITON A-20)."

Replacement paragraph at page 27, lines 24-26:

"Anthracyclines include daunorubicin (formerly daunomycin) and doxorubicin (also referred to herein as [adriamycin] ADRIAMYCIN (doxorubicin HCl). Additional examples include mitozantrone and bisantrene."

Replacement paragraph at page 28, lines 9-12:

"Further examples of cytotoxic agents include, but are not limited to, ricin, bryodin, gelonin, supporin, doxorubicin, [taxol] TAXOL, cytochalasin B, gramicidin D, ethidium bromide, etoposide, tenoposide, colchicine, digydroxy antracin dione, l-dehydrotesteosterone, and glucocoticoid."

Replacement paragraph at page 48, lines 23-29:

"Results of the CDC demonstrate that mutant hBR96-2B has approximately 10 fold less activity than the control hBR96-1 (which has two affinity mutations, one in H2 and one in H3, [refer to previous patent] as shown in provisional patent application Serial

60/023,033 filed August 2, 1996 (Figure 20)). The mutants that have the least ability to kill cells in the presence of complement is hBR96-2C with the triple mutations at positions 318, 320 and 322 and the hBR96-2H mutant (least cytotoxic antibodies in the panel) which contains all six mutations at the three different locations. ADCC activity was most affected by the CH2 deleted hBR96-2 molecule (Figure 21). hBR96-2B and –2H lost between 100 and 1000 fold activity to kill in the presence of effector cells. In the ADCC assay the hBR96-2B molecule also lost approximately 10 fold activity (Figure 21)."

APPENDIX B: Amended Claims with Markings to Show Changes Mad

during due to

1. (Amended) A method for inhibiting immunoglobulin-induced toxicity resulting from immunoglobulin immunotherapy in a subject comprising administering an immunoglobulin molecule to the subject, the immunoglobulin molecule having a variable region and a constant region, the immunoglobulin molecule being modified prior to administration by structurally altering multiple toxicity-associated [domains] regions in the [constant region] CH2 domain so that immunoglobulin-induced toxicity is inhibited.

2. (Twice Amended) A method for inhibiting immunoglobulin-induced toxicity resulting from immunoglobulin immunotherapy in a subject comprising administering a structurally altered antibody to the subject, the structurally altered antibody comprising a variable region and a constant region, multiple toxicity-associated [domains] regions in the [constant region] CH2 domain being modified so as to render the constant region unable to mediate an antibody dependent cellular cytotoxicity response or activate complement thereby inhibiting immunoglobulin-induced toxicity resulting from immunotherapy.

3. (Amended) A method for inhibiting immunoglobulin-induced toxicity resulting from immunotherapy in a subject comprising administering an Ig fusion protein to the subject, the Ig fusion protein having multiple structurally altered toxicity-associated [domains] regions in the [constant region] CH2 domain.

4. (Amended) A method for inhibiting immunoglobulin-induced toxicity resulting from immunotherapy in a subject comprising administering an Ig fusion protein to the subject, the Ig fusion protein comprising a modified constant region, the modification being a structural alteration in multiple toxicity-associated regions within the [CH_2] CH2 domain.

5. (Amended) A method for preventing immunoglobulin-induced toxicity resulting from immunotherapy for a disease in a subject comprising:

(a) selecting an immunoglobulin which recognizes and binds a target, the target being associated with the disease;

(b) mutating the immunoglobulin so selected by structurally altering multiple toxicity-associated [domains] regions in the [constant region] CH2 domain of the immunoglobulin thereby creating a structurally altered immunoglobulin;

(c) administering the structurally altered immunoglobulin of step (b) to the subject under conditions so that the structurally altered immunoglobulin recognizes and binds the target thereby alleviating symptoms associated with the disease [the structural alteration of the constant region thereby preventing immunoglobulin-induced toxicity in the subject].

6. (Amended) A method for preventing immunoglobulin-induced toxicity resulting from immunotherapy for a disease in a subject comprising:

(a) selecting an Ig fusion protein which recognizes and binds a target, the target being associated with the disease;

(b) structurally altering multiple toxicity-associated [domains] <u>regions</u> in the [CH_2] <u>CH2</u> domain of the constant region of the Ig protein so selected;

(c) administering the structurally altered Ig fusion protein of step (b) to the subject under conditions so that the structurally altered Ig fusion protein recognizes and binds the target thereby alleviating symptoms associated with the disease[, the structural alteration of the CH_2 domain thereby preventing immunoglobulin-induced toxicity in the subject].

APPENDIX C: Compl te Set of P nding Claims

1. A method for inhibiting immunoglobulin-induced toxicity resulting from immunoglobulin immunotherapy in a subject comprising administering an immunoglobulin molecule to the subject, the immunoglobulin molecule having a variable region and a constant region, the immunoglobulin molecule being modified prior to administration by structurally altering multiple toxicity-associated regions in the CH2 domain so that immunoglobulin-induced toxicity is inhibited.

2. A method for inhibiting immunoglobulin-induced toxicity resulting from immunoglobulin immunotherapy in a subject comprising administering a structurally altered antibody to the subject, the structurally altered antibody comprising a variable region and a constant region, multiple toxicity-associated regions in the CH2 domain being modified so as to render the constant region unable to mediate an antibody dependent cellular cytotoxicity response or activate complement thereby inhibiting immunoglobulin-induced toxicity resulting from immunotherapy.

3. A method for inhibiting immunoglobulin-induced toxicity resulting from immunotherapy in a subject comprising administering an Ig fusion protein to the subject, the Ig fusion protein having multiple structurally altered toxicity-associated regions in the CH2 domain.

4. A method for inhibiting immunoglobulin-induced toxicity resulting from immunotherapy in a subject comprising administering an Ig fusion protein to the subject, the Ig fusion protein comprising a modified constant region, the modification being a structural alteration in multiple toxicity-associated regions within the CH2 domain.

5. A method for preventing immunoglobulin-induced toxicity resulting from immunotherapy for a disease in a subject comprising:

(a) selecting an immunoglobulin which recognizes and binds a target, the target being associated with the disease;

(b) mutating the immunoglobulin so selected by structurally altering multiple toxicity-associated regions in the CH2 domain of the immunoglobulin thereby creating a structurally altered immunoglobulin;

(c) administering the structurally altered immunoglobulin of step (b) to the subject under conditions so that the structurally altered immunoglobulin recognizes and binds the target thereby alleviating symptoms associated with the disease.

6. A method for preventing immunoglobulin-induced toxicity resulting from immunotherapy for a disease in a subject comprising:

(a) selecting an Ig fusion protein which recognizes and binds a target, the target being associated with the disease;

(b) structurally altering multiple toxicity-associated regions in the CH2 domain of the constant region of the Ig protein so selected;

(c) administering the structurally altered Ig fusion protein of step (b) to the subject under conditions so that the structurally altered Ig fusion protein recognizes and binds the target thereby alleviating symptoms associated with the disease.

8. The method or claim 1 or 5, wherein the immunoglobulin molecule is IgG.

9. The method of claim 1 or 5, wherein the immunoglobulin molecule is IgM.

10. The method of claim 1 or 5, wherein the immunoglobulin molecule is IgA.

11. The method of claim 2, wherein the antibody recognizes and binds Le^y.

12. The method of claim 5, wherein the antibody recognizes and binds Le^x.

13. The method of claim 2, wherein the antibody is a monoclonal antibody BR96 produced by the hybridoma HB 10036 as deposited with the ATCC.

14. The method of claim 2, wherein the antibody is a chimeric antibody ChiBR96 produced by the hybridoma HB 10460 as deposited with the ATCC.

15. The method of claim 1 or 5, wherein the immunoglobulin recognizes and binds Le^y.

16. The method of claim 1 or 5, wherein the immunoglobulin recognizes and binds to Le^x.

17. The method of claim 1 or 5, wherein the immunoglobulin is a monoclonal antibody BR96 produced by the hybridoma HB 10036 as deposited with the ATCC.

18. The method of claim 1 or 5, wherein the immunoglobulin is a chimeric antibody ChiBR96 produced by the hybridoma HB 10460 as deposited with the ATCC.

19. The method of claim 3, 4 or 6, wherein the Ig fusion protein recognizes and binds Le^y.

20. The method of claim 3, 4, or 6, wherein the Ig fusion protein recognizes and binds Le^x.

21. The method of claim 3, 4 or 6, wherein the Ig fusion protein comprises the antigen binding site of monoclonal antibody BR96 produced by the hybridoma HB 10036 as deposited with the ATCC.

22. The method of claim 3, 4 or 6, wherein the Ig fusion protein comprises the antigen binding site of chimeric antibody ChiBR96 produced by HB 10460 as deposited with the ATCC.

28. The method of claim 2, wherein the antibody is conjugated to a cytotoxic agent.

29. The method of claim 1 or 5, wherein the immunoglobulin is conjugated to a cytotoxic agent.

30. The method of claim 3, 4 or 6, wherein the Ig fusion protein is conjugated to a cytotoxic agent.

31. The method of claim 28, wherein the cytotoxic agent is selected from the group consisting of antimetabolites, alkylating agents, anthracyclines, antibiotics, anti-mitotic agents, and chemotherapeutic agents.